Supplemental Material

PBPK /ERDEM Model Equations

The PBPK model was developed on the ERDEM platform, assuming well-perfused distribution to the tissues. For the rapidly perfused tissue, representative of tissues without metabolism or elimination, the fate of chemical *i* is described by

$$V_{RP}\frac{dC_{RP_i}}{dt} = Q_{B,RP}C_{AB,F_i} - Q_{B,RP}\frac{C_{RP,F_i}}{R_{RP,VB_i}}$$

where *V* is the tissue volume, *C* is the chemical concentration, Q_B is the blood flow, and *R* is the partition coefficient. The subscripts *RP* stands for the rapidly perfused tissue, *AB* and *VB* for the arterial and venous blood respectively, and *F* for the free (unbound) portion of the chemical.

The equations for the liver are representative of absorption, metabolism and enzyme inhibition. Chemical *i* is described by

$$V_{LV}\frac{dC_{LV_i}}{dt} = \frac{dA_{ST,PB_i}}{dt} + \frac{dA_{IN,PB_i}}{dt} + Q_{B,LV}C_{AB,F_i} - Q_{B,LV}\frac{C_{LV,F_i}}{R_{LV,VB_i}} - \frac{dA_{LV,E_i}}{dt} - \sum_{j=1}^{N_{M_j}}\frac{dA_{LV,M_{i,j}}}{dt} - \sum_{I_{C,l,m}=i}\frac{dA_{LV,M_{l,m}}}{dt}$$

The equations for the input to portal blood from the stomach and the intestine are respectively:

$$\frac{dA_{ST,PB_i}}{dt} = K_{ABS,ST,PB_i}A_{ST_i},$$

and

$$\frac{dA_{IN,PB_i}}{dt} = K_{ABS,IN,PB_i}A_{IN_i},$$

where *A* is the mass, K_{ABS} is the absorption rate constant, *ST* corresponds to the stomach, *IN* to the intestine, and *PB* to the portal blood. The metabolism in the liver, from chemical *j* to *k*, which could correspond to transformation or production of chemical *i* described here, is represented by

$$\frac{dA_{M,LV_{j,k}}}{dt} = V_{Mx,LV_{j,k}} \frac{C_{LV,F_j}}{\left(K_{mm,LV_{j,k}} + C_{LV,F_j}\right)}$$

where V_{mx} and K_{mm} are the constants for Michaelis-Menten kinetics. Elimination due to inhibition of enzyme j is

$$\frac{dA_{LV,E_i}}{dt} = V_{LV} K_{IN,LV_{i,j}} C_{LV,F_i} E_{LV,F_j}$$

where E is the enzyme concentration and K_{IN} is the bimolecular inhibition rate constant.

Urinary elimination is modeled to take place in the kidney, described by

$$V_{KD} \frac{dC_{KD_i}}{dt} = Q_{B,KD} C_{AB,F_i} - Q_{B,KD} \frac{C_{KD,F_i}}{R_{KD,VB_i}} - \frac{dA_{KD,URN_i}}{dt}$$

where the subscript *KD* corresponds to the kidney and *URN* to urine. The mass excretion rate was modeled as a saturable process

$$\frac{dA_{KD,URN_i}}{dt} = V_{m,KD,URN_i} \frac{C_{KD,F_i}}{(K_{mm,KD,URN_i} + C_{KD,F_i})}$$

where V_m is the maximum rate, and K_{mm} is the saturation constant, similar to the terms in Michaelis-Menten saturable metabolism.

Table 1s. Sensitivity Coefficients

Parameter description	Max. CPF in blood	Max. Free CPF blood	8-hr TCPY U_{ER}	24-hr TCPY U_{ER}
Binding CPF	0.86	-0.11	0.01	0
Cardiac output	0.29	0.29	0.01	0
Km, urine elimination	0	0	-0.84	-0.68
Liver blood flow	0.57	0.57	0	-0.17
Liver volume	0.01	0.01	0	-0.17
Par. coeff. CPF liver:blood	-0.99	-0.98	0.01	0
Part coeff TCPY-g kidney:blood	0	0	0.84	0.51
Part coeff TCPY-g slow perf:blood	0	0	-0.63	-0.51
Rate, intestine to feces	-0.13	-0.12	-0.16	-0.34
Rate, intestine to portal blood	0.48	0.48	0.29	0.17
Slowly perfused tissue volume	0.26	0.26	0.62	0.17
V_{max}, CPF to CPFO	-0.71	-0.70	0	0
V_{max}, CPFO to TCPY	0	0	0.01	-0.17
V_{max}, Urine elimination	0	0	0.85	0.34